

### REMARKS

Applicants respectfully request entry of the amendments hereinabove, reconsideration of the Office Action mailed on November 19, 2003 and allowance of the claims.

#### **35 U.S.C. 112**

Claims 1, 4-10, 14 and 16-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for bombesin antagonists listed on pages 8-35 in the instant specification, does not reasonably provide enablement for other bombesin antagonists.

The rejection states that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The rejection states that in the instant case, the specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. The rejection directs Applicants' attention to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

- 1) the quantity of experimentation necessary,
- 2) the amount of direction or guidance provided,
- 3) the presence of absence of working examples,
- 4) the nature of the invention,
- 5) the state of the prior art,
- 6) the relative skill of those in the art
- 7) the predictability of the art, and
- 8) the breadth of the claims.

The rejection states that Applicant fails to set forth the criteria that define a suitable sexual dysfunction treating "bombesin antagonists". Also, the rejection states Applicant fails to provide information allowing the skilled artisan to ascertain these compounds without undue experimentation. The rejection states that in the instant case, only a limited number of "bombesin antagonists" examples are set forth. The rejection states that it is noted that these examples

are neither exhaustive, nor define the class of compounds required since there is no structural, physical or chemical structures associated with them. The rejection states that the only common properties among them are their capabilities of blocking or antagonizing bombesin receptors. The rejection reasons that the claims are drawn to a method of treating sexual dysfunction by employing potentially any compounds known to men. The rejection also states that because of the lack of guidance to identify which compound is suitable to be used in the instant invention, the skilled artisan would be required to perform undue experimentation to screen for suitable candidate in order to ascertain suitable bombesin antagonist compounds. The rejection states that employment of bombesin receptor antagonists in treating sexual dysfunction is unpredictable, requiring each embodiment to be individually assessed for physiological activity. The rejection also states that the instant claims read on all "bombesin antagonist(s)", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. The rejection concludes that Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

Applicants traverse the rejection under under 35 U.S.C. 112, first paragraph of claims 1, 4-10, 14 and 16-46.

The rejection is based upon the proposition that undue experimentation would be required to practice the method of e.g., claim 1 for bombesin antagonists (other than those described within formula 1). The Examiner noted seven of the eight Wands factors in explaining the rejection. All Wands factors must be considered "in determining whether a disclosure requires undue experimentation..." *In re Wands*, 8 USPQ2d at 1404. Further, the issue on enablement is not whether experimentation, even a considerable amount of experimentation, might be required; the issue is whether the experiments required--in the particular art, with the skill of the art in that field and with the extent and nature of the disclosure at issue--are "undue". *Id.* at 1404; see also MPEP 2164.01(a).

The rejection specifically states that only a limited number of "bombesin antagonists" examples are set forth and that these examples are neither exhaustive, nor define the class of compounds required since there is

no structural, physical or chemical structures associated with them. However, “[i]t is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art.” *Ex parte Obukowica*, 27 USPQ2d 1063, 1067 (Bd. Pat. App. & Interf. 1992) (Exhibit E).

All eight of the Wands factors must be considered by the Examiner. As the MPEP specifically states: “It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the [Wands] factors while ignoring one or more of the others. The examiner’s analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole.” MPEP 2164.01(a).

Applicants will discuss below several of the specific Wands factors which support enablement in this case. Applicants submit that when all of the Wands factors are considered including the specific teachings in the specification and the level of skill in this art as evidenced by the patents and publications cited herein, claim 1 is fully enabled, and this application should be promptly passed to issue. The test for “undue experimentation” is not merely quantitative “since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed” (*In re Wands*, 8 USPQ2d at 1404).

In summary, one skilled in the art, with Applicants’ teachings before him and with due regard to the knowledge in the art as of Applicants’ effective filing date, would be able to practice the full scope of claim 1 at least because: (1) Applicants’ disclosure (specification and original claims) set forth the invention with at least the breadth of claim 1, (2) the specification disclosed multiple examples of useful bombesin antagonists, (3) bombesin antagonists with a wide variety of structures, not limited to those of Formulas I, II or III were known *per se* in the art (*albeit* for different purposes), (4) the art thus knew the structures of numerous bombesin antagonists and how to make them, and the previous known utilities were recognized as due to the bombesin antagonist properties of these compounds, (5) the specification

teaches a procedure, itself known in principle as of the effective filing date, to test for and determine the bombesin, and specifically BB<sub>1</sub> and BB<sub>1</sub> binding characteristics for any given candidate, (6) there is no contrary evidence--and the Examiner has cited none--suggesting that the procedures described in the specification are unusual (they are not) or difficult to carry out (they are well within the skill of the art) and (7) claim 1 is a method claim defining the new use of a *per se* known class of compounds. Applicants will discuss these factors below.

## **I. APPLICANTS' SPECIFICATION**

Applicants' specification plainly taught one skilled in the art that the invention, in its broader aspects, included "the use of a bombesin antagonist... for the treatment of sexual dysfunction in a subject" (page 3, first full paragraph). Thus, in the first instance, the inventors clearly explained their invention in terms that encompassed claim 1 currently at issue. See also page 5, lines 26-27 "Bombesin receptors are present in hypothalamic areas. We have found that they can exert a neuromodulatory effect on sexual behavior.", and page 6, lines 16-19 "The compounds of this invention are useful in the treatment of female sexual dysfunction...." and the sentence bridging pages 6 and 7 "The compounds of this invention are useful in the treatment of male sexual dysfunction....."

The specification also emphasized that the "compounds of the invention are bombesin antagonists" .

The disclosure further discloses over 50 published patent applications that disclose bombesin antagonists (see the specification page 8, last paragraph) and some contain *in vitro* test methods that can be used to determine the bombesin antagonistic activities of candidate compounds. For example, U.S. 5,877,277 discloses an *in vitro* test for inhibition of GRP binding to bombesin receptors, U.S. 5,650,395 discloses a calcium mobilization assay to screen for GRP ligands which possess antagonistic activity, and U.S. 5,068,222 discloses an *in vitro* binding assay which assesses the ability of a test compound to displace radiolabelled GRP from the bombesin receptor is disclosed. The invention description did not merely

refer to these other documents which contain suitable test methods but also set forth the methodology of certain procedures that could be used to determine the antagonist activity of compounds being evaluated for use in the invention (see the specification pages 89-90, Example 28, BB<sub>1</sub> and BB<sub>2</sub> Binding Assays). In addition, actual binding assay data for a plurality of compounds is included in page 90 which can be used for purposes of comparison to any compounds to be tested for bombesin antagonist activity.

Further, the Examples are replete with in vivo test methods for determining the activity of test compounds for the treatment of sexual dysfunction.

These procedures to evaluate candidates were not unique or difficult to carry out and the principles of the test procedures had been taught in the art to determine this characteristic. There is no evidence suggesting that one skilled in the art would have any difficulty in carrying out the procedures.

In light of this illustrative disclosure, Applicants clearly told the art that (a) the invention was the administration of the class of bombesin antagonists and (b) described certain test procedures that could be employed to ascertain the bombesin inhibition characteristics of any candidate compound.

Consequently, even assuming that there is a low level of predictability in the chemical arts (as impliedly argued by the Examiner "The employment of bombesin receptor antagonists in treating sexual dysfunction is unpredictable, requiring each embodiment to be individually assessed for physiological activity"), Applicants' disclosure tells one skilled in the art how to practice the invention, with or without a low level of predictability, and, how to determine bombesin inhibitory activity and how to carry out the full scope of the invention described in claim 1.

**II. LARGE NUMBERS OF BOMBESIN  
ANTAGONISTS OF VARIOUS STRUCTURES  
WERE KNOWN AS OF APPLICANTS' FILING  
DATE**

Applicants were not, and have never claimed to be, the first to describe compounds having bombesin antagonist properties. Attention is directed to the patents and patent applications referenced in pages 8 and 46-47 of the instant application that teach, as of the effective filing date of the instant application, a wide variety of known bombesin antagonists. This further confirms that, as a class, bombesin antagonists with a wide variety of structures well beyond those of Formulas I, II and III (Formulas I, II and III and subgenera are described in the lengthy description of compounds disclosed in the instant application at pages 9-33) were known, as were methods of making and testing them for inhibitory activity. One skilled in the art would have no difficulty in finding other candidate compounds which, based on the fundamental teachings of Applicants' invention, could be used to treat sexual dysfunction.

Applicants submit that the plethora of patents and publications dated prior to their effective filing date teach that as a class, bombesin antagonists, and various sub-types thereof, were known as of Applicants' effective filing date, and there has never been any contention otherwise.

**III. OTHER U.S. PATENTS WITH CLAIMS TO THE  
THERAPEUTIC USE OF CGMP PDE  
INHIBITORS**

The PTO has approved the issuance of patents claiming pharmaceutical compositions and methods which employ Bombesin antagonists in general, without reference to chemical structure. Thus, claim 1 presented by Applicants, is in a breadth and format which have been repeatedly accepted as entirely proper.

An illustrative patent of this type is U.S. 5,650,395, claims 1-22 (treatment of pulmonary hypertension with bombesin antagonists). In fact this

patent is the U.S. counterpart to a reference used by the Examiner in the obviousness rejection (i.e., WO96/28214). Another illustrative patent of this type is U.S. 5,439,884 (blocking fertilization with bombesin antagonists-claims 11-16).

Applicants' claim 1 should be permitted, just as was approved in the above illustrative patents.

#### **IV. CONCLUSION**

When all of the Wands factors-- and many other factors-- are considered, claim 1's full scope has been properly enabled. Although some routine testing may be necessary, this experimentation is not undue. Factors which establish the enablement of claim 1 include (1) the invention was broadly described and initially claimed as not limited to the compounds of claim 12 (Formulas I, II and III), (2) a variety of illustrative compounds were set forth, (3) the art was replete with references to compounds having the ability to act as bombesin antagonists, thus providing structure, method of preparation, method of testing and uses (other than treating sexual dysfunction) based on such inhibition, (4) a specific illustrative testing procedure-- its principles *per se* described in the art-- was set forth in the specification to determine bombesin and, specifically BB<sub>1</sub> and BB<sub>2</sub> binding, (5) claims of the type (bombesin antagonism with no limitation to structure) illustrated by claim 1 have been issued by the PTO and (6) the discovery by Applicants of the claimed use of bombesin antagonists has been subsequently recognized by those of skill in the art.

The experimentation employed here is not undue. This important application has enriched the art. The teachings are broad and highly significant. Claims commensurate with the importance and breadth of the described invention should be allowed.

#### **35 U.S.C. 103(a)**

Claims 1, 4-10, 14, and 16-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Howell et al. (WO 98/07718), WO96/28214, and Hurel

et al. in view of Merck Manual and sildenafil prescribing information (references of record).

The rejection states that Howell et al. (WO 98/07718) teaches a method of treating and/or preventing depression employing an oral pharmaceutical composition/dosage form comprising non-peptide bombesin receptor antagonists (see particularly, abstract, page 10 and claims 11-12).

The rejection states that WO 96/28214 teaches bombesin inhibits smooth muscle contraction, splanchnic vasodilation and bombesin antagonist negates these bombesin-induced biological effects (See page 5, lines 18-38).

The rejection states that Hurel et al. teaches that bombesin-like peptide antagonists have vasoactive properties (see page 1243).

The rejection admits that Howell et al. (WO 98/07718) and Hurel et al. taken together do not particularly teach the employment of bombesin-like peptide and/or non-peptide antagonists in a method of treating sexual dysfunction. The rejection admits that neither do they teach the combination of vasodilators, neurotransmitter antagonists and/or agonists or a hormone like compound in its method of treating sexual dysfunction.

The rejection states that the Merck Manual teaches depression, low testosterone level and vascular abnormalities as causes of sexual dysfunction (see pages 1575 and 1577-78).

The rejection states that Sildenafil is known as a PDE5 inhibitor vasodilator employed in the treatment of sexual dysfunction (see pages 5-6).

The rejection states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ bombesin-like peptide and/or non-peptide antagonists in a method of treating sexual dysfunction. The rejection states that it would also have been obvious to combine the bombesin receptor antagonist with vasodilators, neurotransmitter antagonists and/or agonists or a hormone like compound in a method of treating sexual dysfunction.

The rejection reasons that one of ordinary skill in the art would have been motivated to employ bombesin-like peptide and/or non-peptide antagonists in a method of treating sexual dysfunction because (1) they are known to be employed in methods of treating depression which is known to be an underlying



cause of sexual dysfunction; (2) they are known to be vasoactive which are known to be useful in treating sexual dysfunction. The rejection reasons that one of ordinary skill in the art would have also been motivated to combine the bombesin receptor antagonist with vasodilators, neurotransmitter antagonists and/or agonists or a hormone like compound in a method of treating sexual dysfunction since they are all known to be useful in treating sexual dysfunction. The rejection also concludes that combining agents that are known to be useful for the same purpose in a combination composition to be used for the same purpose is known to be within the skill of the artisan and therefore, obvious, see *In re Kerkhoven* 205 USPQ 1069.

#### ***Examiner's Response to Applicants' Arguments***

The rejection states Applicant's arguments filed August 4, 2003 averring Hurel not teaching bombesin antagonist as vasodilators have been fully considered but they are not persuasive. The Response directs Applicants' attention to the discussion above in regard to the teachings of WO96/28214.

The rejection states that Applicant's arguments filed August 4, 2003 averring even bombesin-like peptide as useful to treat hypertension, the prior art does not provide reasonable expectation of success have been considered, but are not found persuasive. The rejection also states that the teaching of the cited prior art clearly provides the reasonable expectation of success in two ways: (1) they are known to be employed in methods of treating depression which is known to be an underlying cause of sexual dysfunction; (2) they are known to be vasoactive which are known to be useful in treating sexual dysfunction.

The rejection states that Applicant's further arguments filed August 4, 2003 averring even bombesin-like peptide as useful to treat depression, the prior art does not provide a reasonable expectation of success since some antidepressants cause sexual dysfunction have been considered, but are not found persuasive. The rejection reasons that the antidepressants that are causing sexual dysfunction are through a specific neurological pathway, e.g., serotonin reuptake inhibitors usually cause sexual dysfunction. The rejection states that there is no teachings of record to provide the reason that bombesin receptor antagonist will cause sexual dysfunction in the same way as some of the antidepressants do. The rejection states that teaching away has to be clear.

The rejection concludes that there is no clear teaching away present in the references of record.

Applicants traverse the rejection of Claims 1, 4-10, 14 and 16-23 under 35 U.S.C. 103(a) as being unpatentable over Howell et al. . (WO 98/07718), WO96/28214 and Hurel et al. in view of Merck Manual and sildenafil prescribing information (references of record).

Initially, Applicants note the admission that Howell et al and Hurel et al. taken together do not particularly teach the employment of bombesin-like peptide and/or non-peptide antagonists in a method of treating sexual dysfunction.

The art of record is insufficient to support a *prima facie* case.

When all of the relevant art is taken together as a whole (as it must be in assessing obviousness), the art actually teaches away from the claimed use. There is no suggestion that bombesin antagonists would be useful for the treatment of sexual dysfunction, and there is no reasonable expectation of success taught by the art were bombesin antagonists to be tried for the treatment of sexual dysfunction. At best, the art supports only an "obvious to try" situation (which Applicant does not concede).

Applicants submit their invention is not "obvious to try", but even assuming *arguendo*, that the claims are "obvious to try" that is not the standard for patentability.

Applicants submit that the art of record and extrapolations therefrom are speculative and do not provide a legally sufficient basis to support a *prima facie* case that the administration of bombesin receptor antagonist inhibitors are useful for the treatment of sexual dysfunction. Further, the art does not provide a reasonable expectation of success, without which Applicants' invention cannot be obvious even if it were "obvious to try" (which is denied).

It is Applicants' position that "obvious to try" is not the standard for patentability, and that the Examiner did not make out a *prima facie* case because, *inter alia* (1) the references provide no effective motivation or suggestion that the administration of bombesin receptor antagonist inhibitors as a class could or would be useful for the treatment of sexual dysfunction and (2) even allowing, *arguendo*, that any such suggestion or motivation is provided, the

references provide absolutely no expectation of success. The law is emphatic that “obvious to try” is not the standard for patentability.

“Obvious to try” is NOT the test of obviousness under 35 U.S.C. §103. American Hospital supply Corp. v. Travenol Laboratories, Inc., 223 USPQ 577, 582 (Fed. cir. 1984). The Federal Circuit has explained the proper test:

The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out **and would have a reasonable likelihood of success**, viewed in light of the prior art. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant’s disclosure** (emphasis added).

In re Dow Chemical Co., 5 USPQ.2d 1529, 1531 (Fed. Clir. 1988); Amgen, Inc. V. Chugai Pharmaceutical Co. Ltd. 18 USPQ.2d 1016. 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

As explained fully in the sections which follow, the art cited by the Examiner, at most, makes it no more than perhaps obvious to explore the area of bombesin receptor antagonist inhibitors generally (e.g., for the treatment of pulmonary hypertension or depression, but certainly not for sexual dysfunction), and this is one of the classic hallmarks of an “obvious to try” rejection:

“The admonition that ‘obvious to try’ is not the standard under §103 has been directed mainly at two kinds of error. In some cases, what would have been ‘obvious to try’ would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful...**In others, what was ‘obvious to try’ was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.**”

In re O’Farrell, 7 USPQ2d 1673, at 1681, (Fed. Cir. 1988), emphasis supplied.

It is further noted that “[t]he issue of obviousness is determined entirely with reference to a hypothetical person having ordinary skill in the art. It is only that hypothetical person who is presumed to be aware of all the prior art. The actual inventor’s skill is irrelevant to the inquiry, and this is for a very important reason. The statutory emphasis is on a person of ordinary skill. Inventors, as a

class, according to the concepts underlying the Constitution and the statutes that have created the patent system, possess something -- call it what you will - which sets them apart from the workers of ordinary skill, and one should not go about determining obviousness under section 103 by inquiring into what patentees (i.e. inventors) would have known or would likely have done, faced with the revelations of references. A person of ordinary skill in the art is also presumed to be one who thinks along the line of conventional wisdom in the art and is not one to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights, it makes no difference which." Standard Oil Co. V. American Cyanamid Co., 774 F.2d 448, 454 (Fed. cir. 1985).

Further, even if the art is, *arguendo*, viewed as providing a suggestion, it provides no reasonable expectation or likelihood of success. Thus, even if an argument could be made that the art provides a suggestion to explore the use of bombesin receptor antagonist inhibitors generally to treat sexual dysfunction, this amounts, perhaps, to inviting experimentation, i.e., to perhaps making testing bombesin receptor antagonist inhibitors obvious to try, which again is manifestly not the standard for patentability. O'Farrell, *supra*.

Applicants submit that while WO 98/07718 is stated to teach a method of treating depression with a bombesin receptor antagonist it does not follow that there is a suggestion or a reasonable likelihood of success (both a suggestion and a reasonable likelihood of success are requirements for a prima facie case in this instance) that a bombesin receptor antagonist will be useful for the treatment of sexual dysfunction. In fact, the WO 98/07718 reference teaches away from the use of a depression treatment for the treatment of sexual dysfunction since it is well known that many anti-depressants cause sexual dysfunction. Applicants submit that they have reviewed the Merck Manual 17th edition at the pages cited by the Examiner and could not find the passages referred to (i.e., the "Merck Manual teaches depression, low testosterone level and vascular abnormalities as causes of sexual dysfunction"). However, even assuming that such passages occur, Applicants submit that the Merck Manual (17th edition) page 1557 lists side effects of antidepressants as a cause of hypoactive sexual desire disorder. This passage does not specify certain types of antidepressants, it merely refers to the class of drugs as a whole. Further,

page 1558 Table 192-1 lists different classes (the antidepressants -selective serotonin reuptake inhibitors and tricyclic antidepressants) of drugs as possible causes of sexual dysfunctions. This state of the art hardly constitutes the motivation to try other antidepressants for the treatment of sexual dysfunction or that there would be a reasonable likelihood of success that bombesin receptor antagonists would be effective for the treatment of sexual dysfunction. Accordingly, even assuming *arguendo* that depression can be a cause of sexual dysfunction it is not clear that there is a reasonable expectation that all cures for depression would result in a treatment for concomitant sexual dysfunction. It is clear that antidepressants can cause sexual dysfunction and that there is no reasonable expectation from the prior art that the administration of an antidepressant would positively impact sexual dysfunction.

Further, the knowledge that bombesin antagonists are antidepressants coupled with the knowledge that antidepressants cause sexual dysfunction suggests that bombesin antagonists may cause sexual dysfunction. This clearly contradicts the rejection reasoning that one would be motivated to employ bombesin antagonists in a method of treating sexual dysfunction because they are known to be employed in methods of treating depression which is known to be an underlying cause of sexual dysfunction. Applicants submit that the inference that bombesin antagonists may cause sexual dysfunction clearly negates the motivation suggested in the rejection.

The rejection responded to the Applicants' previous response stating that "only certain classes of antidepressants will cause sexual dysfunction, such as SSRI, and the newer generation of tricyclic antidepressants" and "Absent any evidence that Bombesin antagonists will interact with those neurotransmitter systems, one would still be motivated to employ bombesin antagonists to treat depression and thereby treat sexual dysfunction secondary to depression" Applicants submit that while the fact that antidepressants may cause sexual dysfunction does not prove or guarantee that Bombesin antagonists may cause sexual dysfunction it certainly raises a serious question whether Bombesin antagonists may cause sexual dysfunction (thus negating any reasonable likelihood of success that bombesin antagonists would be useful for the treatment of sexual dysfunction). It is known that serotonin (5-HT) levels in the

brain can be elevated by SSRI's, thereby treating depression but, as a side-effect, can cause sexual dysfunction. Since bombesin antagonists also raise serotonin levels, it could be assumed by one of skill in the art that such bombesin antagonists could also have anti-depressant activity (as demonstrated in WO 98/07718 and therefore also cause sexual dysfunction). This suggestion, that bombesin antagonists could cause sexual dysfunction since they raise serotonin levels, clearly negates a reasonable expectation of success that bombesin antagonists would be useful to treat sexual dysfunction. However, surprisingly, Applicants have found this is not the case as bombesin antagonists can, in fact, treat sexual dysfunction. Thus, the cited art would teach away from the present invention. Restated, the fact that certain classes of antidepressants will cause sexual dysfunction clearly does not provide a reasonable likelihood of success that Bombesin antagonist antidepressants would be useful for the treatment of sexual dysfunction (in fact it suggests the opposite) . Again, the case law described above mandates that a reasonable likelihood of success is a necessary element of a prima facie case.

Applicants submit that WO 96/28214 states that "bombesin inhibits smooth muscle contraction, splanchnic vasodilation" and that bombesin antagonists may be useful for the treatment of pulmonary hypertension or for use in lowering pulmonary systolic pressure (see claims 1 and 2). These statements do not suggest that bombesin antagonists would be useful for the treatment of sexual dysfunction. To the contrary, there is no reasonable expectation of success that agents that lower pulmonary systolic pressure would be useful for the treatment of sexual dysfunction. As stated before a reasonable expectation of success is necessary for a prima facie case in this instance.

Applicants submit that the Hurel et al. reference does not teach that bombesin-like peptide antagonists have vasoactive properties. Thus, Hurel et al. suggests the mere exploration of the use of bombesin receptor antagonist inhibitors as a treatment of pulmonary hypertension, and this is one of the classic hallmarks of an "obvious to try" rejection. The Hurel et al. reference clearly states that "The preliminary study suggests that these peptides have acute haemodynamic effects in the pulmonary vasculature.....Further studies are required." Applicants submit that the use of the term "suggests" and the

statement that further studies “are required” is the hallmark of a suggestion for the exploration of a scientific area. It does not even provide a reasonable likelihood of success that the one bombesin antagonist tested is a vasodilator since it states that further studies are required. This is not sufficient to make a prima facie case.

In addition, Hurel et al. only discloses the testing of one bombesin-like antagonist on one subject. This at most provides the suggestion of trying bombesin like antagonists for the treatment of pulmonary hypertension. One skilled in the art would not have a reasonable likelihood of success from the testing of one compound since the perceived effect could be caused by some other activity of the compound besides the bombesin antagonist activity. Further, one skilled in the art would not have a reasonable likelihood of success from the testing of one subject since there could have been a variety of complex factors that lead to any perceived result.

It is thus respectfully submitted that the Hurel et al. reference is an article which perhaps supplies some interesting academic research tidbits. The mere mention of the word “pulmonary hypertension” amounts to conjecture or speculation, and most certainly does not provide a “reasonable expectation of success”, even if “obvious to try” (which is denied), as required under US patent law for obviousness.

Further, Applicants submit that Hurel et al. does not provide basis for a general teaching that bombesin-like peptide antagonists have vasoactive properties or act as systemic vasodilators. The reference describes patients suffering from pulmonary hypertension (high blood pressure in the lungs). Hurel et al hypothesized that the bombesin-like peptide GRP has vasoactive properties within the innermost layer of the pulmonary artery (pulmonary endothelium) and that a GRP antagonist might have a beneficial effect. While upon administration of a bombesin antagonist pulmonary systolic and diastolic blood pressure were reduced, there was a rise in systemic blood pressure (see Table). Clearly the suggestion that bombesin receptor antagonists increase systemic blood pressure would not motivate one to use such compounds to treat sexual dysfunction. An increase in systemic blood pressure would teach away from the use of bombesin antagonists to treat sexual dysfunction.

The Hurel et al work is further described in the corresponding Hurel WO96/28214 and US 5650395, copies of which have been previously submitted and have been made of record. Hurel refers in 5650395 at column 1 line 36 onwards to an autonomous endocrine system within the lungs termed the pulmonary neuroendocrine system that had been shown to secrete gastrin-related peptide, and claims the use of a bombesin antagonist *only* in relation to the medical indication of lowering pulmonary systolic pressure. Thus claim 1 of the issued US patent reads:

“A method of lowering the pulmonary systolic pressure of a subject suffering from pulmonary hypertension, said method comprising administering to the subject an amount of a bombesin antagonist, said amount being effective to lower the systolic pressure.”

Thus, at best the Hurel et al. art when taken as a whole may suggest bombesin antagonists are useful for the indication of lowering pulmonary systolic pressure but does not suggest that a bombesin antagonist is effective as a peripheral vasodilator and clearly would not motivate one to use a bombesin antagonist to treat sexual dysfunction.

Even if Hurel et al had provided a general teaching of vasoactive properties (which is denied) that would not lead the skilled person to conclude that the disclosed compound might be used in the treatment of sexual dysfunction. Antihypertensive medications may cause erectile dysfunction either by drug-specific effects or by decreasing the systolic pressure and thereby increasing the intracavernosal penile pressure. This result is especially prevalent in patients with diabetes or hypertension who have an underlying microvascular disease. The *Merck Manual of Geriatrics* comments in Chapter 115, Sexual Dysfunction in Men ([http://www.merck.com/pubs/mm\\_geriatrics/sec14/ch115.htm](http://www.merck.com/pubs/mm_geriatrics/sec14/ch115.htm)):

“About 25% of cases of erectile dysfunction are caused by drugs ... especially antihypertensives (most notably reserpine,  $\beta$ -blockers, guanethidine, and methyl dopa) ...”

As a further example, benzazepril (Captopril), which is an ACE inhibitor used for the treatment of high blood pressure and congestive heart failure, may



give rise in men to reduced libido and more rarely impotence (see <http://www.healthcentral.com/mhc/top/001803.cfm>).

Finally, clearly, Hurel et al. does not mention or suggest in any way the treatment of sexual dysfunction.

Claims 24-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Howell et al. (WO 98/07718), WO 96/28214, and Hurel et al. in view of Merck Manual and sildenafil prescribing information, references of record as applied to claims 1, 4-10, 14 and 16-23 above, and further in view of Leiblum (International Journal of Impotence Research, 1998; 10 (Suppl 2):21045-S106, Levin (Exp. Clin. Endocrinol., 1991;98(2);61-69), Gioco et al (US Patent 5,565,466).

The rejection states that Leiblum teaches different sexual disorders are affected by either mood disorder such as depression, which would reduce the desire of sexual activities, or vascular factors such as decreased vaginal lubrication which can cause pain during intercourse and female arousal disorder (see particularly page S105, col. 1, second paragraph - col. 2 and pages S106, col.1).

The rejection states that Levin teaches VIP can increase the vaginal lubrication and induce arousal in female patients (see particularly the abstract).

The rejection states that Gioco et al. teaches a method of modulating the excitory phase of male and female sexual response using vasodilating agents such as phentolamine, yohimbine,  $\alpha$ -adrenergic vasodilator, and imipramine (See col. 12, line 11 to col. 13, line 31, 45, and 66, Examples 3 and 4; also particularly claims 14 and 17).

The rejection reasons that it would have been obvious to one of the ordinary skill in the art at the time the invention was made to combine the herein secondary agent with bombesin antagonist in a method of treating sexual dysfunction.

The rejection reasons that one of ordinary skill in the art would have been motivated to combine the herein secondary agents with bombesin antagonist in a method of treating sexual dysfunction because various sexual dysfunction are known to be affected by various factors such as depression and vascular. The rejection reasons that combining the herein claimed secondary agents, which

are known to correct and treat the under lying conditions that negatively affect sexual activities individually, with bombesin antagonist into a single composition for the very same purpose would be obvious (see *In re Kerkhoven* 205 USPQ 1069), absent evidence to the contrary.

Applicants traverse the rejection of Claims 24-46 (as amended) under 35 U.S.C. 103(a) as being unpatentable over Howell et al. (WO 98/07718), WO96/28214 and Hurel et al. in view of the Merck Manual and sildenafil prescribing information, references of record as applied to claims 1, 4-10, 14 and 16-23 above, and further in view of Leiblum (International Journal of Impotence Research, 1998, 10(Suppl 2): S104-S106), Levin (Exp. Clin. Endocrinol., 1991;98(2):61-69), Gioco et al. (US Patent 5,565,466).

Applicants submit that, at least for the reasons provided above in response to the rejection of claim 1 and dependent claims thereof, claims 24-46 (as dependent claims) are not obvious in light of the plethora of references cited by the rejection. Applicants further note that the rejection of claims 24-46 relies upon at least 5 references in combination and as many as 7 references in combination and Applicants submit that such a multiplicity of a combination of references appears to be based upon the impermissible use of hindsight.

Please charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 16-1445. Two copies of this sheet are enclosed.

Respectfully submitted,

Date: \_\_\_\_\_

5/17/2004



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